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Risk of death and the efficacy of eritoran tetrasodium (E5564): Design considerations for clinical trials of anti-inflammatory agents in sepsis*

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In this issue of *Critical Care Medicine*, Tidswell et al (1) report the results of a randomized, multicenter phase II trial of eritoran tetrasodium (E5564), a synthetic competitive lipopolysaccharide inhibitor. Three hundred septic patients were first stratified based on Acute Physiology and Chronic Health Evaluation II (APACHE II) scores into groups with either low (20%–50%) or high (50%–80%) predicted mortality rates. Subjects were then randomized to receive either a low or high dose of E5564 or placebo for 6 days. Twenty-eight-day mortality rates in the low- (32.0%) and high- (26.6%) dose E5564 groups were lower than placebo (33.3%) independent of predicted mortality, but this difference was not statistically significant ($p = .335$). The investigators note increasing control mortality rates with increasing APACHE II scores (0%, 32%, 37%, and 56% for quartiles 1 to 4, respectively). Importantly, as risk of death (i.e., control mortality rate) increased across these quartiles, the odds ratio of survival with both low- and high-dose E5564 increased as well, in relationships that were significant ($p = .025$ for both doses) (Fig. 1). As the investigators reported, despite the relatively small numbers of patients in each quartile, high-dose E5564 was associated with clearly trends toward harm in the lowest quartile but benefit in the highest ($p = .08$ and $.11$, respectively).

Of note, trials of other anti-inflammatory agents, recombinant human activated protein C (rhAPC), and corticosteroids demonstrated a similar relationship between treatment effect and risk of death in sepsis. A metaregression analysis of published preclinical and clinical trials of six different mediator-specific anti-inflammatory agents, as well as prospective preclinical investigations of such agents, showed benefit when risk of death was high but decreasing efficacy and even harm as risk decreased (2, 3). Although published preclinical studies tested these agents against highly lethal septic challenges and showed significant benefit, overall treatment effects were substantially diminished in clinical trials with lower control mortality rates. After Food and Drug Administration analysis of the pivotal rhAPC trial showed the drug's benefit was evident primarily in high-risk patients (APACHE II 25), the agency's approval of rhAPC was restricted to this subgroup (4–6). Finally, recent meta-analyses of low-dose corticosteroid use in sepsis indicate that this therapy's efficacy may also relate to risk of death (7, 8). Similar to this previous experience, while E5564 showed convincing benefit in highly lethal preclinical sepsis models (control mortality rates

of 60%–90%), potential benefit in the present clinical study is only evident in high-risk subgroups (1, 9, 10).

If E5564 proves beneficial in high-risk septic patients, but portends harm in low-risk patients, practitioners must clearly understand whether and in which low-risk patients the diminution of E5564's efficacy may cross over to a potential harmful effect. A trend toward increased hepatobiliary and renal complications overall with E5564 in the trial by Tidswell et al may provide a basis for potentially worse outcomes with treatment in the low-risk patients. Data from this study also suggest that only patients with a predicted mortality rate of 50% might benefit from E5564 (Fig. 1). Clearly, an agent with a broad therapeutic window will be far more useful than one that is safe and beneficial only in the sickest septic patients. Furthermore, if an agent's efficacy varies based on underlying risk of death, then precise criteria for defining the risk–benefit ratio and the appropriateness of administration in individual patients must be defined. Although treatment with rhAPC is frequently based on the APACHE II score in the United States and the number of injured organs in Europe, neither system was ever prospectively tested for such use. In the Administration of Drotrecogin Alfa (Activated in Early Stage Severe Sepsis) trial, patients with APACHE II scores ≥ 25 , who should have had improved survival with rhAPC based on Food and Drug Administration recommendations, did not (11). Even in the Tidswell study, although the APACHE II score was expected to select patients with mortality rates ranging between 20% and 80%, the observed range was lower. Another stratification tool currently used—the presence of ongoing vasopressor-dependent shock—also remains unproven (7, 12). Finally, if risk of death influences E5564's efficacy within the strict confines of a randomized, controlled trial, widespread clinical use would surely alter the relationship. Clinical surveys have shown that rhAPC is routinely administered to patients with APACHE II scores lower than FDA recommendations (5, 13, 14). Complicating matters, the predictive ability of the APACHE II scores is influenced by patient case mix, location and the time of measurement, each of which will vary to a greater degree during clinical use than in a randomized, controlled trial (15–19).

Tidswell et al report a phase III trial of E5564 is currently underway that limits enrollment to patients with a significant risk of mortality (APACHE II scores ≥ 21). Although this design may demonstrate efficacy for E5564, it may not establish whether the agent poses harm, has no effect, or is beneficial for patients with a lower risk of death. Concurrent conduct of preclinical studies exploring this relationship could begin to address this question. Additionally, the ongoing phase III trial could be amended to include patients with APACHE II scores <21 , with strict provisions for frequent and vigilant safety monitoring. If all risk groups were studied together, a smaller sample size could determine whether differing treatment trends based on predicted risk of death confirm concerns raised by the phase II trial. Analysis of such data would also more clearly delineate the scope of a relationship between risk of death and E5564's effects, if present. Even with such measures, extensive phase IV testing may be essential to appropriately narrow the target population of E5564.

The failure of anti-inflammatory agents to demonstrate convincing benefits in sepsis is thought to relate in part to patient heterogeneity. Sepsis-associated risk of death contributes to this heterogeneity, and evolving experience suggests it may play a pivotal role in calibrating this therapeutic approach. Inflammation represents an interconnected group of host responses to infection. When it is excessive, inflammation overshadows the effects of the underlying infection and in itself causes a higher mortality rate. Thus, in this scenario, inhibiting even a single inflammatory mediator may be sufficient to depress this interconnected response and improve outcome. Conversely, when inflammation is appropriate and protective for a majority of subjects, disrupting this necessary host response

may be harmful. Recognizing and investigating the potential influence of risk of death during the preclinical and clinical evaluation of anti-inflammatory agents like E5564, although requiring careful oversight and additional resources, may greatly improve the ability of physicians to safely and effectively administer these treatments in septic patients.

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Figure 1.

The regression lines in this figure show the relationship between control odds and the odds ratio of survival with low- (45 mg) or high- (105 mg) dose E5564 alone (*A* and *B*, respectively) or overall (*C*) comparing patients with increasing predicted mortality rates based on Acute Physiology and Chronic Health Evaluation II quartiles 1, 2, 3, or 4. Using analysis previously described (2), the control odds for each quartile were calculated based on the observed control mortality rate (i.e., control mortality rates of 10%, 50%, or 90% equal control odds of 0.1, 1, or 10, respectively). The odds ratios of survival are shown as circles with 95% confidence intervals delineated by the vertical lines. The effects of both high- and low-dose E5564 were similar and appear directly related to the risk of death (i.e., control odds). Both doses were most beneficial in the Acute Physiology and Chronic Health Evaluation II quartile with the highest control mortality rate, but this benefit declined as control mortality rate decreased and was no longer evident in the quartile with the lowest mortality rate. The correlation between effect and control odds was high ($r = 0.97$ for each), and the relationship was significant ($p = .025$ for the slopes of all three regression lines). These relationships were calculated based on data available from the final manuscript (high-dose E5564) or during its review (low-dose E5564).